

Chapter 9: Pneumococcal Disease

Cynthia G. Whitney MD, MPH and Martin Cetron MD

I. Disease description

Streptococcus pneumoniae infections are among the leading causes worldwide of illness and death for young children, persons with underlying debilitating medical conditions, and the elderly. Pneumococcal disease is the most commonly identified cause of bacterial pneumonia; since the widespread use of vaccines against *Hemophilus influenzae* type b, it has become the most common cause of bacterial meningitis in the United States.¹ Each year in the United States, pneumococcal disease accounts for approximately 3000 cases of meningitis, 50,000 cases of bacteremia, 125,000 cases of pneumonia requiring hospitalization, and 7–10 million cases of otitis media.^{2,3} Approximately 10% of all patients with invasive pneumococcal disease die of their illness,³ but case-fatality rates are higher for the elderly and patients with certain underlying illnesses. *Pneumococcus* accounts for more deaths than any other vaccine-preventable bacterial disease.⁴

II. Background

A vaccine against the 23 most common serotypes of *S. pneumoniae* has been available since the early 1980s, and the Advisory Committee on Immunization Practices (ACIP) recommends that it be administered to persons ≥ 2 years of age who have any of several underlying medical conditions and to all persons 65 years of age or older.³ Despite its availability, the vaccine is underutilized. Data from the Behavioral Risk Factor Surveillance System indicate that in 1997, only 45.4% of persons ≥ 65 years of age had ever been vaccinated; however, this figure does represent an increase from 36.9% in 1995.⁵ Non-Hispanic whites were more likely to have received vaccine than African-Americans and Hispanics.

Resistance to penicillin and other antimicrobial agents has spread rapidly in the United States. In some areas, more than 30% of pneumococcal isolates are not susceptible to penicillin.

Several pneumococcal conjugate vaccine formulations are in development and evaluation phases. In contrast to the currently available 23-valent vaccine made of bacterial capsular polysaccharide, conjugate vaccines made of polysaccharide linked to a protein carrier promise to be effective in infants and young children. Preliminary data from a large randomized trial of a 7-valent pneumococcal conjugate vaccine among infants and children enrolled in a large northern California health maintenance organization show a high degree of efficacy for prevention of invasive pneumococcal disease.⁶ Several other large randomized trials assessing the efficacy of conjugate vaccines to prevent invasive infection, pneumonia, and acute otitis media in infants are ongoing. A 7-valent conjugate vaccine may be licensed in the United States for use in young children in 2000.

In the past, *S. pneumoniae* was almost uniformly susceptible to penicillin, allowing most physicians to treat persons with severe infections with penicillin alone, without testing for antibiotic resistance. However, since the late 1980s, resistance to penicillin and other antimicrobial agents has spread rapidly in the

United States.^{7,8} Data from CDC's Emerging Infections Program/Active Bacterial Core Surveillance (ABCs) indicate that resistance to penicillin and other antimicrobial drugs is a worsening problem in many areas.² The prevalence of resistant strains can vary markedly by region and between hospitals within the same region. In some areas of the United States, over 30% of isolates are not susceptible to penicillin. A smaller yet substantial percentage of isolates is also resistant to multiple antimicrobial drugs. The proportion of pneumococcal illnesses caused by drug-resistant *S. pneumoniae* (DRSP) among children may be higher than that among adults, and the incidence of drug-resistant infections can change rapidly.⁹ Outbreaks due to susceptible *S. pneumoniae* and DRSP have been reported in child-care centers and among residents of long-term-care facilities in which pneumococcal vaccine coverage was low.¹⁰⁻¹²

The emergence of DRSP has made treatment of pneumococcal disease more difficult. Because of a lack of rapid, sensitive, and specific diagnostic tests, therapy for both invasive disease and milder illnesses such as otitis media remains empiric. Groups of experts have made recommendations for treating infections commonly caused by pneumococcus in an era of increasing prevalence of DRSP. Guidelines for otitis media¹³ and pneumonia¹⁴ call for clinicians to base empiric therapy decisions on whether DRSP is likely to be causing the illness; therefore, knowledge of local susceptibility patterns may be helpful. However, local prevalence data often are lacking.

Because of inadequate surveillance data and the limitations of current diagnostic testing, clinicians may prescribe therapy for suspected pneumococcal infections that is not indicated or is unnecessarily broad. Inappropriate empiric or prophylactic antimicrobial use contributes to the development of DRSP. Recent principles have been developed to encourage judicious use of antimicrobial agents for children with upper respiratory infections.¹⁵

III. Importance of surveillance

Goals of surveillance for DRSP include defining and monitoring the prevalence and geographic distribution of DRSP and enabling rapid recognition of new resistance patterns. Surveillance information can be used on the national level for research and policy development and at the state or local level to raise awareness of DRSP among clinicians and the general public. Surveillance data also may be useful for tracking the impact of interventions aimed at reducing unnecessary use of antimicrobial agents or improving vaccination coverage. There are currently several systems used to track DRSP in the United States. Although surveillance has traditionally been the responsibility of public health organizations, private industry also has begun to fund and operate systems to monitor drug resistance.

Since 1979, CDC has operated a national sentinel surveillance system for invasive pneumococcal disease. This system was created to estimate pneumococcal vaccine efficacy by tracking the distribution of serotypes causing disease among vaccinated and unvaccinated persons. The sentinel system includes voluntary reporting of all invasive *S. pneumoniae* disease cases and

submission of isolates from 12–15 hospital microbiology laboratories in the United States. The laboratories report directly to CDC and send the isolate from each patient to CDC for serotyping and, until 1995, antimicrobial susceptibility testing. The Invasive *Streptococcus pneumoniae* Surveillance Report Worksheet (Appendix 15) includes demographic and clinical information such as vaccination history and whether the patient survived the infection. Although this system was designed primarily to track vaccine efficacy, the antimicrobial susceptibility data from participating hospitals were used to determine that DRSP increased in the United States in the early 1990s and was used to track DRSP until 1995.^{7,8}

In 1994, CDC began tracking invasive pneumococcal disease using ABCs.¹⁵ This system collects information from eight areas on all cases of pneumococcal disease in which the bacteria were isolated from a normally sterile site, such as blood or cerebrospinal fluid (CSF). ABCs is population based, meaning that all cases within each surveillance area are identified. Surveillance personnel contact area microbiology laboratories about twice monthly to identify cases; a review of laboratory records is conducted every 6 months to ensure that no cases are missed. Isolates are sent to CDC or to collaborating reference laboratories for susceptibility testing and serotyping. ABCs personnel collect information such as demographics, diagnosis, underlying medical conditions, and outcomes for each case patient. In addition to providing surveillance information, ABCs serves as an infrastructure for additional epidemiologic research.

In 1994, the Council of State and Territorial Epidemiologists (CSTE) recommended that states adopt mandatory reporting of invasive infections caused by DRSP. By 1996, 16 states and a large city health department had made DRSP a laboratory-reportable condition in order to track the prevalence of drug resistance among invasive isolates of *S. pneumoniae*.¹⁷ As of 1998, 37 states were conducting some surveillance for DRSP.¹⁸ States have used a variety of methods to track DRSP. While the CSTE case definition does not require reporting of all invasive isolates, this is desirable to calculate the prevalence of DRSP. Surveillance that includes all invasive isolates also would enable more complete analysis of the impact of new conjugate vaccines after licensure and of campaigns to increase the use of the 23-valent pneumococcal polysaccharide vaccine.

To facilitate reporting, electronic laboratory reporting has been proposed as a method that could capture all incident cases of invasive pneumococcal disease along with the isolate's antibiogram directly from hospitals' laboratory information systems, without the need for paper reporting forms. Electronic laboratory reporting systems for DRSP and other reportable conditions are currently being piloted in several states.

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IV. Disease reduction goals

Disease reduction goals focus on minimizing complications of DRSP infections through prevention and control of DRSP infections. A vaccine for the 23 most common serotypes of *S. pneumoniae* is available, yet underutilized. Healthy

People 2000 objectives target the vaccination of 60% of persons at risk for pneumococcal illness by the year 2000.¹⁹ However, aggregate data from the National Health Interview Survey for the United States indicate that only 45.4% of persons ≥ 65 years of age had been vaccinated in 1997; no individual state had reached the goal of 60% coverage.⁵ A number of factors contribute to the insufficient use of vaccine. Methods such as the use of standing orders in clinics and hospitals and simultaneous administration of pneumococcal vaccine with influenza vaccine have been shown to improve vaccine utilization.³

V. Case definitions

The CSTE case definition was intended to monitor only invasive pneumococcal infections and their antimicrobial susceptibility patterns. For this system, invasive pneumococcal infection refers only to meningitis and bacteremia, identified by isolation of *S. pneumoniae* from CSF or blood.

Confirmed case. A confirmed case of DRSP is defined as isolation of *S. pneumoniae* from a normally sterile site (e.g., CSF or blood) in a patient with invasive pneumococcal disease in which the isolate is nonsusceptible (using National Committee for Clinical Laboratory Standards [NCCLS] methods and breakpoints) to antimicrobial drugs currently approved for treating pneumococcal infections.²⁰

When oxacillin disk screening is the only antimicrobial susceptibility method used, the antimicrobial susceptibility profile cannot be definitely determined. For these instances, a definition for a probable case is needed.

Probable case. A probable case of invasive DRSP is defined as isolation of *S. pneumoniae* from a normally sterile site (e.g., CSF or blood) in a patient with invasive pneumococcal disease in which the isolate is nonsusceptible by oxacillin screening (i.e., zone size ≤ 19 mm) and no further antimicrobial susceptibility testing has been performed. Oxacillin screening is highly sensitive and specific for detecting beta-lactam-resistant *S. pneumoniae*; however, resistance to non-beta-lactam antibiotics is not detected with this screening method (see "Laboratory testing").

A confirmed case of drug-resistant S. pneumoniae is defined as either meningitis or bacteremia in which S. pneumoniae cultured from CSF, blood, or other normally sterile site is identified as non-susceptible.

VI. Laboratory testing

Diagnosis of pneumococcal infection is confirmed by the recovery of *S. pneumoniae* from a normally sterile body site (e.g., blood, CSF, pleural fluid, or peritoneal fluid). Because pneumococci frequently colonize the upper respiratory tract in the absence of disease, the clinical significance of recovering the organism from nonsterile body sites (e.g., expectorated sputum, conjunctiva) is less certain. Gram stain may be helpful in interpreting cultures of expectorated sputum; finding a predominance of gram-positive diplococci and >25 leukocytes with <10 epithelial cells per high power field on microscopic examination supports the diagnosis of pneumococcal pneumonia.

All isolates of S. pneumoniae from normally sterile sites should be screened using a 1-mg oxacillin disk; non-susceptible isolates should have further quantitative testing.

Based on recommendations from the NCCLS, all isolates of *S. pneumoniae* from normally sterile sites should be tested for penicillin resistance in hospital laboratories.²⁰ Pneumococcal resistance to penicillin can be screened initially by using a 1-mg oxacillin disk; penicillin resistance is considered probable with an oxacillin zone size <20 mm. The screening approach is highly sensitive (99%) and specific (80%–90%) and should detect nearly all isolates resistant to penicillin and extended-spectrum cephalosporins. Isolates found to be nonsusceptible by oxacillin disk should then be subjected to quantitative testing for drugs that may be used to treat the patient. In the diagnosis of life-threatening pneumococcal infections, NCCLS also encourages laboratories to go directly to quantitative MIC testing without first screening by oxacillin disk. In all instances, clinicians should alter therapy based upon the results of antimicrobial susceptibility testing; when appropriate, broad-spectrum therapy should be switched to a narrow-spectrum agent to which the isolate is susceptible.

VII. Reporting

Participating laboratories report cases of DRSP to their local or state health department with information on the patient's date of birth or age, the anatomic site of specimen collection, the date of specimen collection, the antimicrobial susceptibility pattern, and unique identifiers for the laboratory and the specimen. To accurately calculate the prevalence of DRSP, it is highly desirable for the laboratory to report all cases of invasive pneumococcal infection along with the antibiogram of the *S. pneumoniae* isolate. Such a change in the case reporting requirements has been adopted or is under consideration in several states. An additional benefit of doing surveillance for all invasive pneumococcal disease is the ability to track the progress of vaccine efforts to reduce the incidence of *S. pneumoniae* infections.

VIII. Vaccination

The 23-valent pneumococcal polysaccharide vaccine is approximately 60% efficacious for the prevention of invasive pneumococcal infection.^{21,22} A dose of vaccine should be administered to all persons at increased risk of serious pneumococcal infection because of underlying medical conditions and to all persons ≥ 65 years of age.³ A single revaccination after at least 5 years should be considered for persons with functional or anatomic asplenia and persons with immunocompromising conditions. Previously vaccinated persons should be vaccinated at 65 years of age, providing at least 5 years has passed since the first dose. Pneumococcal vaccine may be administered concurrently with influenza vaccine by separate injection in the opposite arm.

The 23-valent vaccine is not adequately immunogenic in young children; thus, it is not recommended for use in children <2 years of age, a population at high risk for acute pneumococcal otitis media, bacteremia, and meningitis. Licensure of the 7-valent pneumococcal conjugate vaccine is anticipated to occur during 2000. Following licensure, the ACIP will issue recommendations for the vaccine's use in young children.

IX. Enhancing surveillance

There are a number of surveillance activities that can improve the detection and reporting of cases and the comprehensiveness and quality of reporting.

Establish nationwide reporting of DRSP. Concern about increasing resistance to antimicrobial agents has prompted many health departments to institute regulations requiring laboratories to report DRSP isolates. To provide clinicians with local surveillance data and to assist with planning and evaluating public health interventions, establishing surveillance systems in all states would be optimal. Systems currently in use employ a variety of surveillance methods; because of the different methodologies, aggregating data from all states is difficult. Studies are needed to identify optimal surveillance methods to track DRSP that would allow aggregation of data from multiple areas.

Improve the detection of DRSP in laboratories by promoting appropriate interpretive standards for identification and susceptibility testing of *S. pneumoniae*. On the basis of NCCLS interpretive standards, all isolates of *S. pneumoniae* from usually sterile sites should be tested for penicillin resistance. Laboratory capacity needed for this testing should be developed and maintained.

Develop an electronic, laboratory-based reporting system capable of reporting DRSP and other conditions. Population-based laboratory reporting is necessary to reflect accurately the local geographic and temporal trends in DRSP because there is geographic variation in resistance to antimicrobial drugs among and within communities. To decrease the burden (e.g., time, staffing) to laboratory personnel, any system for laboratory-based reporting should use existing computerized data that might be already stored electronically in a laboratory information system. The system should allow for feedback of information to the laboratory, state and local health departments, CDC, and health-care providers.

X. Case investigations

As with most respiratory pathogens, rapid, sensitive, and specific diagnostic tests are not available; thus, early in the course of illness, diagnosis of *S. pneumoniae* infection is usually presumptive and the choice of antimicrobial therapy is nearly always empiric. However, once *S. pneumoniae* is isolated from a normally sterile body site, antimicrobial susceptibility testing is necessary for patient management. Case investigations are not usually warranted, except in outbreaks or as determined by the state health department. ❖

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